

REMARKS

Claims 120, 121, 124 to 128, 131 to 133, 136 to 154, and 157 to 167 were pending in this patent application. Claims 125, 126, 128, 131 to 133, 141, 142, 144 to 147, 150 to 154, and 157 to 167, previously withdrawn from consideration as drawn to non-elected subject matter, and claims 139, 140, 143, 148, and 149 are hereby canceled without prejudice or disclaimer. Claims 120, 121, 124, 127, and 136-138 remain pending. Solely to advance prosecution Claims 120, 121, 124, 137, and 138 are hereby amended. No claims have been added. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 120, 121, 124, 127, 136 to 140, 143, 148, and 149 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Lee, et al., *Cell*, 1993, 75, 843-854 ("the Lee article"), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 ("the Manche article"), published PCT application number WO 94/01550 ("the Agrawal application"), and U.S. Patent Number 5,801,154 ("the Baracchini patent"). Applicants respectfully request reconsideration and withdrawal of this rejection.

To establish *prima facie* obviousness, the Patent Office must identify "an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006).

The present rejection is not supported by a reason why one of skill in the art would have combined the teachings of the cited references to arrive at the present invention. To further establish facts concerning the cited art, applicants provide herewith the Declaration of David Corey, Ph.D. Dr. Corey, an expert in the field, explains the cited art and establishes, among other things, that there would have been no reason to combine the cited references to arrive at the present claims.

Independent claim 120 recites compositions comprising a duplex consisting of first and second chemically synthesized oligonucleotides that are not covalently linked to each other. Each of the oligonucleotides consists of 17 to 25 linked nucleosides, and the first oligonucleotide is 100% complementary to the second oligonucleotide and to a target mRNA. The first

oligonucleotide is a gapmer with a gap of at least 4 nucleosides having 2'-OH groups, and each nucleoside of the wings has a 2' modification. The cited references, when considered individually or in combination, fail to provide a reason for making such compounds.

The Lee article describes two endogenous transcripts encoded by the *C. elegans lin-4* gene: *lin-4L*, which is approximately 61 nucleotides in length and forms a stem-loop structure; and *lin-4S*, which is approximately 22 nucleotides in length and is identical to the first 22 nucleotides of *lin-4L*. See, e.g., the abstract and page 847, second column. These molecules are partially complementary to another *C. elegans* transcript, *lin-14*. The Lee article fails to describe or suggest duplexes comprising two separate, 100% complementary oligonucleotides each consisting of 17 to 25 linked nucleosides where one is 100% complementary to a target mRNA. See the Declaration of David Corey at paragraph 15. Moreover, since the molecules in the Lee article are endogenous transcripts, nothing in Lee suggests chemical modification of such oligonucleotides. See Declaration of David Corey, Ph.D., at paragraph 14.

The Manche article similarly fails to provide a reason to make the claimed oligonucleotides. See Declaration of David Corey, Ph.D., at paragraph 19. The article describes experiments for studying the interferon-induced protein kinase DAI using RNA duplexes consisting of pairs of oligonucleotides of 15, 23, 34, 40, 55, 67, 85, or 104 nucleosides. See, e.g., the abstract and figure 1. The duplexes that were 15 and 23 nucleotide pairs in length failed to elicit DAI activity and Manche speculates that duplexes shorter than 33 base pairs will not be active. Accordingly, there would be no reason to undertake further experiments with duplexes of oligonucleotides of the lengths claimed (17-25). See the Declaration of David Corey, Ph.D., at paragraph 16. Moreover, the Manche article provides no reason to use duplexes in which one oligonucleotide is complementary to a target mRNA or to incorporate modifications. See paragraphs 17 and 18.

The Agrawal application also fails provide a reason to make the claimed oligonucleotides. See Corey Declaration at paragraphs 25-28. Instead, the Agrawal application, e.g. at page 5, lines 13 – 17, describes single-stranded, self-hybridizing oligonucleotides useful for RNase H-based antisense. As explained in Dr. Corey's declaration at paragraphs 25 – 28, the Agrawal application fails to describe or suggest complementary pairs of oligonucleotides consisting of first and second oligonucleotides that are not covalently linked to each other, as claimed.

Finally, the Baracchini patent likewise fails to provide a reason to make the claimed compounds, and thus fails to compensate for the deficiencies of the Lee and Manche articles and the Agrawal application. As Dr. Corey explains at paragraph 24 of his declaration, the Baracchini patent describes single-stranded RNase-H based antisense oligonucleotides. The Baracchini patent fails to teach or suggest duplexes of two separate 100% complementary oligonucleotides each consisting of 17 to 25 linked nucleosides, and thus fails to describe or suggest the claimed oligonucleotides.

Dr. Corey explains that none of the cited references individually -- nor all of them together -- provides a reason for making the claimed compounds. Without relying on the teaching in the present specification, which identifies a double-strand-specific RNase, the Office has not provided any reason for making the claimed compounds. Thus, the claimed subject matter would not have been obvious at the time of the invention. Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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